UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,249	12/17/2001	**Manuel Vega**	119365-00002 / 911	7196

20985 7590 05/13/2008
FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
LIN, JERRY	
ART UNIT	**PAPER NUMBER**
1631	

MAIL DATE	DELIVERY MODE
05/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/022,249	VEGA ET AL.	
	Examiner	Art Unit	
	Jerry Lin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10,14,15,17-33 and 42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-10,14,15,17-33 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments and amendments, filed February 7, 2008, have been fully considered and they are persuasive. However, in light of the amendments, the following rejections and/or objections are newly applied as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-3, 5-10, 14, 15, 17-33, and 42-44 are under examination.

Claim Rejections - 35 USC § 112, 2nd Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-10, 14, 15, 17-33, and 42-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claims 1, 22, 23, 24, 27 and 30 were amended to include the limitation of "the encoded amino acid residues are each replaced along the full-length of the encoded protein or along the full length of a pre-selected domain of the encoded protein so that all position along the full-length or a domain of the protein are individually modified for screening". The instant claims recited that the encoded proteins differ from other encoded proteins by only one amino acid. However, the amendment states that each amino acid residue in an encoded protein or domain is replaced with another

amino acid. However, if each amino acid residue was replaced along the entire length of the encoded protein, then the encoded proteins would differ by more than one amino acid and could not be modified forms of the same protein. Thus, the claims appear to contradict themselves. Clarification via clearer claim language is requested. Claims 2, 3, 5-10, 14, 15, 17-21, 25, 26, 28, 29, 31-33, and 42-44 are rejected for depending from claims 1, 22, 23, 24, 27 and 30.

This rejection was necessitated by amendment.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-3, 5-10, 14, 15, 17-23, 27, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. (US 5,223,409) in view of Wells et al. (US 6,013,478) and in view of Pedersen et al. (WO01/32844).

The instant claims are drawn to a method of producing a plurality of separate sets of nucleic acid molecules where each set of nucleic acid molecules differ from another set of nucleic acid molecules by one codon and the protein encoded on each set differ by one amino acid from the protein encoded on another set. The nucleic acid molecules are then introduced into host cells and an addressable array of these host cells is created where the location of each host cell and nucleic acid molecule is known. The host cells express the proteins and the proteins are individually screened to identify which proteins have a predetermined property that is a chemical, physical, or biological property or activity.

Regarding claims 1, 22, and 23, Ladner et al. teach a method of producing a plurality of separate sets of nucleic acid molecules that encode modified forms of a target protein (column 31, lines 39-68), wherein the nucleic acid molecules in each set are produced by changing codons (column 31, lines 39-68); and each set of molecules encode a proteins that differ from proteins encoded by other sets by the changed codons (column 31, lines 39-68). Ladner further teaches that each molecule may be individually introduced into a host cell where the identity of the nucleic acid molecule is known (column31, line 9-23).

Although Ladner et al. teach that after picking several residues of a protein to vary and then picking only one of those residues to vary (i.e., varying a protein by only

one amino acid) (paragraph bridging columns 11 and12), Ladner et al. does not explicitly teach where the encoded proteins in each set of nucleic acid molecules differ from encoded proteins in another set of nucleic acid molecules by one amino acid.

Regarding claims 1, 22, 23, and 42, Wells et al. teach a method where a residue substituted DNA sequence encodes a residue substituted polypeptide where each polypeptide contains a single substitution at a different amino acid within the active domain (i.e. where each protein encoded by a nucleic acid molecule set differs from the other proteins by only one amino acid and where the amino acid residues are replaced along the full-length of the pre-selected domain) (column 15, line 51-column 16, line 11; expressing the encoded proteins (column 13, lines 36-53); and screening the encoded proteins for a predetermined property that differs from the target protein by at least a 100% change (i.e. two-fold increase or decrease in Kd as compared to the parent protein) (column 17, lines 29-43); identifying each mutated protein as a hit and a designated hit position (i.e. active amino acid residues) (column 17, lines 29-43).

Although, Ladner et al. and Well et al. teach individually introducing a nucleic acid molecule into a host cell where the identity of the nucleic acid molecule is known (Ladner et al., column 31, lines 9-23; Wells et al., column 13, lines 36-53), neither Ladner et al. nor Wells et al. teach creating an array of the host cells.

Regarding claims 1, 22, and 23, Pedersen et al. teach a method of creating an array of host cells in a spatial array so that each location is occupied by a cell (abstract; page 37, lines 24-35); expressing the encoded protein (page 37, lines 24-35; page 40, lines 16-24); individually screening each encoded protein for a predetermined property

that his a chemical, physical or biological property or activity (page 43, line 30-page 45, line 6).

Regarding claims 2 and 10, Wells et al. disclose where the nucleic acid molecules are individually designed and synthesized (column 13, lines 23-36; column 14, lines 40-63).

Regarding claims 3, 5, and 6, Pedersen et al. teach wherein each cell is deposited at a locus in an addressable array (abstract; page 37, lines 24-35) that comprises a solid support with loci containing or retaining cells (e.g. micorotiter plate) (page 37, lines 19-23).

Regarding claims 7, 8, 9, and 27, Wells et al. teach wherein the vectors may be plasmids or viral vectors (i.e. phase particles) (column 14, lines 12-29); and where the host cells are bacterial cells or eukaryotic cells (column 13, lines 26-63). Furthermore, Wells et al. teach modifying the nucleic acid molecules that encode the hits to produce more nucleic acid molecules by replacing codons in a hit position to produce nucleic acid molecules that differ by at least one codon (i.e., proteins that differ by one amino acid residue) (column 15, lines 50-11; column 17, lines 44-60); introducing the nucleic acid molecules into cells and screening the proteins for a predetermined activity (column 13, lines 36-53; column 17, lines 29-43; column 18, lines 25-43).

Regarding claims 14, 15, 43, and 44, Wells et al. teach where the pre-selected codon may encode any of the 19 naturally occurring amino acids (column 16, Table II).

Regarding claim 17, Wells et al. teach that after identifying two or more active amino acid residues (i.e. identifying nucleic acid molecules encoding the leads) (column

15, line 50-column 16, line 11; column 17, lines 35-60; column 17, lines 60-10), the parent nucleic acid molecule may be modified to reflect these two or more active amino acid residues (i.e. recombining the nucleic acid molecules encoding the leads) (column 17, line 60-column 18, line 10), introducing the nucleic acid molecules into cells (column 13, lines 36-53); and screening the cells to identify nucleic acid molecules that encode new leads that exhibt a greater change in property or activity (column 18, lines 17-24).

Regarding claims 18-20, Wells et al. disclose where there are two or more leads (column 15, line 50-column 16, line 11; column 17, lines 35-60; column 17, lines 60-10); where the recombining is done via sit-direct mutagenesis (column 14 ,lines 40-63); where the modifications are effected in a selected domain (column 17, line 60-column18, line 25).

Regarding claim 21, Ladner et al. disclose where the modifications may be done along the full length of the target protein (column 10, lines 54-60).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods of Ladner et al., Wells et al., and Pedersen et al. to gain the benefit of identifying individual active amino acid residues as well as a high throughput screening method. Ladner et al. teaches a generic method of utilizing directed evolution of a target protein. However, Wells et al. teaches that in order to identify the individual amino acid residues involved in a biding domain, a plurality of residue substituted polypeptides are created, each containing a single substitution of an amino acid residue within the active domain (column 17, line 60-column 16, line 11). Thus one of ordinary skill in the art seeking to use Ladner et al.'s method to identify

active amino acid residues, would initially create polypeptides that differ by one amino acid at the binding domain. Furthermore, in order to screen all of these polypeptides, one of ordinary skill in the art would be motivated to use a high-throughput screening method as taught by Pedersen et al. which offers the advantage of a practical and reliable method for the identification of novel substances with new properties from a large number of molecules (page 37, lines 19-24). Thus, one of ordinary skill in the art would have been motivated to combine the methods of Ladner et al., Well et al. and Pedersen et al. for the reasons above.

The instant rejection was necessitated by amendment.

Note:

5. Applicants have stated that the instant claims have been amended to incorporate the limitations of cancelled claim 16. The Examiner disagrees. The instant claims where amended to include the limitation of "the encoded amino acid residues are each replaced along the full-length of the encoded protein or along the full length of a pre-selected domain of the encoded protein so that all position along the full-length or a domain of the protein are individually modified for screening". In contrast, cancelled claim 16 recited "wherein the nucleic molecules of step (e) are produced by systematically replacing each codon that is a hit position, with a codon encoding another amino acid, to produce nucleic acid molecules each different by at least one codon and encoding modified hits to identify leads". Cancelled claim 16 does not recite any limitation regarding the full-length of the encode protein or pre-selected domain.

Furthermore, the amendments do not recite any limitation regarding step (e) or hit positions. Thus, the instant claims have been amended with a new limitation.

In addition, the amendment of "whereby the identity of each set of nucleic acid molecules in host cells of each locus in the array is known" is also a limitation that was not previously present in the claims.

6. Claims 24, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. (US 5,223,409) in view of Wells et al. (US 6,013,478) in view of Pedersen et al. (WO01/32844) as applied to claims 1-3, 5-10, 14, 15, 17-23, 27, 43 and 44 above, and further in view of Berlioz et al. (US 5,925, 565).

The instant claims are drawn to a method of producing a plurality of separate sets of nucleic acid molecules where each set of nucleic acid molecules differ from another set of nucleic acid molecules by one codon and the protein encoded on each set differ by one amino acid to another protein encoded on another set. The nucleic acid molecules are then introduced into host cells and an addressable array of these host cells is created where the location of each host cell and nucleic acid molecule is known. The host cells express the proteins and the proteins are individually screened to identify which proteins have a predetermined property that is chemical, physical, or a biological property or activity. In particular, the instant claims include using eukaryotic cells or assessing the titer of viral vectors.

Ladner et al., Wells et al., and Pedersen et al. are applied as above.

However, Ladner et al., Wells et al., and Pedersen et al. do not teach assessing the titer of viral vectors.

Berlioz et al. teach assessing the titer of viral vectors after transfection for each set of eukaryotic cells (column 14, lines 39-65), and where the viral vector encodes for a protein involved in viral replication (column 5, lines 35-65).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the methods taught by Ladner et al., Wells et al., and Pedersen et al. with Berlioz et al. in order to study the effects of the protein in an eukaryotic setting. Berlioz et al. teaches a method that allows eukaryotic cells, such as a human cell, to express a desired protein (column 6, lines 5-22) for the purpose of producing a therapeutic treatment (column 7, lines 15-25). Ladner et al., Wells et al., and Pedersen et al. methods teach screening for different proteins that exhibit a desired biological, chemical, or physical property. Thus one of ordinary skill in the art seeking to create a new therapeutic treatment, would be motivated to use Giver et al. and Blazquez et al.'s methods to design a product and use Berlioz et al.'s method to express the protein in an eukaryotic cell.

7. Claims 25, 26, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. (US 5,223,409) in view of Wells et al. (US 6,013,478) in view of Pedersen et al. (WO01/32844) in view of Berlioz et al. (US 5,925, 565) as applied to claims 1-3, 5-10, 14, 15, 17-23, 27, 32, 33, 43 and 44 above, and further in view of Drittanti et al. (Gene Therapy (2000) Volume 7, pages 924-929)

The instant claims are drawn to a method of producing a plurality of separate sets of nucleic acid molecules where each set of nucleic acid molecules differ from another set of nucleic acid molecules by one codon and the protein encoded on each set differ by one amino acid to another protein encoded on another set. The nucleic acid molecules are then introduced into host cells and an addressable array of these host cells is created where the location of each host cell and nucleic acid molecule is known. The host cells express the proteins and the proteins are individual screened to identify which proteins have a predetermined property that is chemical, physical, or a biological property or activity. In particular, the instant claims are drawn to a method of determining the titer using real time virus titer and tagged replication and expression enhancement.

Ladner et al., Wells et al., Pedersen et al., and Berlioz et al. are applied as above.

However, Ladner et al., Wells et al., Pedersen et al. and Berlioz et al. do not teach real-time virus titering or tagged replication and expression enhancement.

Drittanti et al. teaches real time virus titering (page 925); using tagged replication and expression enhancement (page 926, right column); and where the process is automated and computer controlled (page 925, left column under Figure 1).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the methods of Ladner et al., Wells et al., Pedersen et al., and Berlioz et al. with Drittanti et al. to gain the benefit of determining the effectiveness of viral vectors. Berlioz et al. teach that one of his goals is to create an effective and

stable viral vector (column 1, lines 10-17). Part of their method requires that they assess the titer of the viral vectors after transmission. Drittanti et al.'s method provides further insight into the stability and efficacy of the vector by offering real time titering. Thus one of ordinary skill in the art would be motivated to combine the methods of Ladner et al., Wells et al., Pedersen et al., and Berlioz et al. with Drittanti et al. in order to gain the benefit of assessing the stability and efficacy of viral vectors.

9. Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al., Wells et al. and Pedersen et al., as applied to claims 1-3, 5-10, 14, 15, 17-23, 27, 43 and 44 above, and further in view of Persson et al. (Journal of Virology (1985) Volume 54, pages 92-97).

The instant claims are drawn to a method of producing a plurality of separate sets of nucleic acid molecules where each set of nucleic acid molecules differ from another set of nucleic acid molecules by one codon and the protein encoded on each set differ by one amino acid to another protein encoded on another set. The nucleic acid molecules are then introduced into host cells and an addressable array of these host cells is created where the location of each host cell and nucleic acid molecule is known. The host cells express the proteins and the proteins are individually screened to identify which proteins have a predetermined property that is chemical, physical, or a biological property or activity. In particular, the instant claims use Hill analysis.

Ladner et al., Wells et al., and Pedersen et al. are applied as above.

However, Ladner et al., Wells et al., and Pedersen et al. do not teach using Hill Analysis.

Persson et al. teach a method that uses the Hilll analysis (i.e. Hill coefficient) for determining the rate in which host cells are infected with viruses (abstract, page 94) or fitting an output signal to a cure representative of a target protein and a test compound (page 94).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Ladner et al., Wells et al., and Pedersen et al. with the method of Persson et al. to gain the benefit of determining if the plasmids or vectors are infecting the host cells. Ladner et al. and Wells et al. teach creating host cells with desired nucleic acids. In such a method, it would be desirable to determine the rate of infection in order to determine how to structure an experiment (e.g., incubation times, concentration, etc.). Persson et al. provide a method of determining the rate of infection. Thus one of ordinary skill in the art would be motivated to combine the methods of Ladner et al., Wells et al., and Pedersen et al. with the method of Persson et al. to gain the benefit of determining the rate of infection of host cells to structure his experiments.

Withdrawn Rejections

10. Applicant's arguments and amendments, filed February 7, 2008, with respect to the rejections made under 35 U.S.C. §103 utilizing the references of Giver et al. and Blazquez et al. have been fully considered and are persuasive. The references do not

teach the amended limitations of producing proteins that differ by one amino acid along the full length of a target protein or a pre-selected domain of the target protein or where the identity of each of the nucleic acid molecules in the host cells are known in an array. Furthermore, the rejection made in the previous office action, under 35 U.S.C. §112 2nd paragraph have been overcome by the amendments. These rejections have been withdrawn.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571)272-2561. The examiner can normally be reached on 7:00-5:30pm, M-TH.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. L./
Examiner, Art Unit 1631

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631